

AMENDMENTS TO THE DRAWINGS

The attached sheet(s) of drawings include changes to Figure 10.

Attachment: Replacement sheet
 Annotated sheet showing changes

REMARKS

Claims 1-16 are pending. Claims 3, 6, and 7 are cancelled. Claims 1, 2, 4, 5, and 8-16 are currently amended. Applicants submit that no new matter has been added as a result of this amendment; support therefor can be found throughout the specification and original claims.

As an initial matter, it is noted that the Office Communication mailed on January 8, 2008, objected to the submission on October 25, 2007. As the Office Communication is understood, the Examiner requires clarification as to the arguments submitted in support of enablement and written description. Accordingly, those portions of the submission of October 25, 2007, have been revised below, to accommodate the Examiner's request.

Information Disclosure Statement

The Examiner asserts at page 3 of the Office Action that the listing of references presented at pages 21-22 of the instant specification is not a proper information disclosure statement. The references listed at those pages are not believed to be material to patentability. Thus, they have not been cited in an information disclosure statement.

Priority

Applicants have amended the specification to include a reference to all related prior applications. Applicants previously identified the prior applications in the application transmittal papers and in the duly executed Declaration. The information concerning the benefit claim was recognized by the Office as shown by its inclusion on the first official Filing Receipt. In view of the above, a petition under 37 CFR 1.78(a) and surcharge under 37 CFR 1.17(t) are not required.

Drawings

In response to the Examiner's objection to Figure 10, Applicants submit herewith a corrected replacement Figure that includes the X-axis label.

Claim Objections

The Examiner objected to claims 1, 4-5, 7, 9, and 10 for various informalities. Claim 5 has been cancelled. Applicants submit that in view of the amendments to claims 1 and 5, the recited objections are rendered moot. Claims 4 and 10 have been appropriately amended to address each of the informalities.

The Examiner asserts at page 7 of the Office Action that the term "Kozak sequence", recited in claim 9, must be referred to by its sequence identification number to comply with 37 CFR 1.821. The instant specification states at page 4, paragraph 0081 of US 2004/0268432 that "Kozak sequence, which is a sequence for effectively translating mRNA in eukaryote (Kozak, 1989) is attached prior to the initiation codon." The Kozak et al. reference cited in the instant specification presents the consensus Kozak sequence. Further, the Kozak sequence is included as part of the sequence of the designed refre1 nucleic acid presented in Figure 9 and SEQ ID NO: 1 of the instant application.

Applicants submit that the Kozak sequence (ACCATGG) is well known in the art. In fact, this sequence is readily identified in a Google Search by searching for "Kozak sequence."

In view of the teachings of the instant specification and further in view of the knowledge available to one of skill in the art regarding the consensus Kozak sequence Applicants submit that it is not necessary to refer to this sequence by a sequence identification number. Indeed, the claims are abundantly clear and definite as recited.

In view of all of the above, Applicants respectfully request reconsideration and withdrawal of the rejections.

Claim Rejections

Rejection of Claims 1-16 under 35 U.S.C. §112, second paragraph

Claims 1-16 are rejected under 35 U.S.C. §112, 2nd paragraph, for alleged indefiniteness.

Claims 3, 6 and 7 have been cancelled.

Additionally, without acquiescing to the grounds for rejection, Applicants have amended the noted claims as follows to clarify the features of the invention.

The Examiner rejected claims 1-2, 7 and 9-12 as “being indefinite in the recitation of the term “gene.” Applicants acknowledge that the Examiner has suggested that “gene” be amended to “coding sequence.” For clarity, Applicants have amended the claims to replace the term gene with the term “nucleic acid encoding a protein.”

The Examiner rejected claim 1 and dependent claims thereof for allegedly being indefinite for omitting essential steps. Applicants have amended claim 1 to clarify the features of the invention.

The Examiner rejected claims 1, 5 and 15 for recitation of the phrase “gene of another species.” Applicants have amended the claims to delete the phrase “gene of another species.”

The Examiner rejected claims 1, 3, 4 and 5 for recitation of the phrase “region of a factor.” Claim 3 is cancelled. Applicants have amended claims 1, 4 and 5 to delete the phrase “region of a factor.”

The Examiner rejected claim 1 for recitation of the term “substantially.” Applicants have amended claim 1 to delete the term “substantially.”

The Examiner rejected claim 2 for recitation of the term “derived.” Claim 2 has been amended to recite “the method according to claim 1, wherein the heterologous nucleic acid is derived from yeast.”

A definition for the term “derived” is not provided in the specification. Therefore, this term should be given its plain, ordinary and accustomed meaning as understood to one of ordinary skill in the art in view of the specification. “Derived” is defined by Webster’s Ninth New Collegiate Dictionary as “to obtain from a specified source.”

The Examiner has rejected claim 16 for the recitation “plant is seed”. Claim 16 has been amended to recite “a seed produced by the plant according to claim 15.”

In view of all of the above, Applicants respectfully request reconsideration and withdrawal of the rejections.

Rejection of Claims 1-16 under 35 U.S.C. §112, first paragraph

Enablement

The Examiner has rejected claims 1 – 16 under 35 U.S.C. §112, 1st paragraph, it being alleged that the specification, “while being enabling for modified yeast FRE1 coding sequence as defined in SEQ ID NO: 1...does not reasonably provide enablement for the scope of possible gene sequences from any species claimed for use in plants.” (Office Action, p.10). Applicants respectfully traverse the rejection.

The claims have been amended to recite specific polyadenylation signal sequences. Amended claim 1 recites “wherein the polyadenylation signal sequence is selected from the group consisting of ATTTA, NATAAA, ANTAAA, AANAAA, AATNAA, AATANA and AATAAN of which N is A, G, C or T.” The claims have also been amended to recite “the GT rich sequence is 8 or more consecutive G and/or T nucleotides.”

In view of the amendments to claim 1, and given the teachings of the specification and the knowledge available to one of skill in the art, one skilled in the art could easily identify the polyadenylation signal sequences and the GT rich sequences encompassed by the claims, for example by using a computer program or by manual analysis of a sequence.

The MPEP states that the determination that “undue experimentation” would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing a combination of factual considerations: the breath of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples, and the quantity of experimentation necessary. In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404. Accordingly, the following factors are considered:

Working Examples and Guidance Provided

According to the MPEP at 2164.02, "compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed." Moreover, "an applicant need not have actually reduced the invention to practice prior to filing. In *Gould v. Quigg*, 822 F.2d 1074, 1078, 3 USPQ 2d 1302, 1304 (Fed. Cir. 1987). The Court held that "the mere fact that something has not previously been done clearly is not, in itself, a sufficient basis for rejecting all applications purporting to disclose how to do it." 822 F.2d at 1078, 3 USPQ2d at 1304 (quoting *In re Chilowsky*, 229 F.2d 457, 461, 108 USPQ 321, 325 (CCPA 1956)). "The specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation. In *reBorkowski*, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970)."

The Examiner admits that "the specification as filed teaches making modifications of the yeast FRE1, specifically making instant SEQ ID NO:1, for use in plants." (Office Action, p.11). The Examiner admits that "(t)he specification teaches transgenic tobacco plants expressing modified yeast FRE1...(that) exhibited functional enzymatic activity" and points out Figure 1 – 18 and Examples 1 – 9. (Office Action, p.11 - 12). However, the Examiner argues that "the specification as filed does not provide any other example genes which would require such modification other than the yeast FRE1 gene for expression in tobacco." (Office Action, p.12). The Examiner argues that "other than a vague teaching to look for GT-rich areas in any such gene, and change the sequence to remove certain sequences, one of skill in the art would not immediately envision what is otherwise any possible nucleic acid gene sequence as broadly claimed." (Office Action, p.13). Applicants disagree.

The specification clearly sets forth requirements for methods for transforming a useful plant by introducing another gene into the useful plant as set forth in the instant invention. For example, at paragraph [0024] the specification teaches:

The base sequence of the nucleic acid of the present invention is a modified base sequence which can be expressed in the transformed useful plant with high

efficiency, and, for example, is a factor relating to the poly(A) addition of mRNA of the said useful plant, and is characterized in that a part of factor relating to the said poly(A) addition is replaced by the other base sequence, further the said base sequence has small G- and T-rich region of the base in the gene to be introduced, has small difference between G- and C-content of the base throughout the gene to be introduced, has no ATTTA sequence and/or preferably the upstream of the initiation codon of the gene to be introduced has Kozak sequence.

Moreover, at paragraph [0054] the specification teaches:

We have found that in a transformed plant, factors affecting expression of introduced gene may be a base sequence which determines addition of poly(A) of mRNA. Further, we have found that in the upstream of the base sequence, which defines addition of poly(A), GT-rich base sequence is necessary. Namely, in the presence of GT-rich base sequence, addition of poly(A) is determined in plants, subsequently mRNA is split at the position after 10-30 bp from the poly(A) signal, for example AATAAA like base sequence, then poly(A) is added by an action of poly(A) polymerase. Accordingly, in case that the introduced gene has such the base sequence, in the transgenic plants, full length mRNA can not be expressed, and mRNA is split in the position after 10-30 bp from the poly(A) signal having AATAAA like base sequence.

Finally, the specification provides numerous examples of transgenic tobacco plants expressing introduced genes (see e.g. examples 1 – 9).

Accordingly, the specification clearly sets forth factors that affect the expression of introduced genes in plants, and moreover have provided working examples directed to such methods. Clearly, the requirements for enablement are met in this case.

State of the Art and Analysis of the Issues

According to the MPEP at 2164. 05(a), “(t)he state of the prior art is what one skilled in the art would have known, at the time the application was filed, about the subject matter to which the claimed invention pertains (and) the state of the art for a given technology is not static in time. It is entirely possible that a disclosure filed on

January 2, 1990, would not have been enabled. However, if the same disclosure had been filed on January 2, 1996, it might have enabled the claims. Therefore, the state of the prior art must be evaluated for each application based on its filing date.”

The Examiner alleges that “other than a vague teaching to look for GT-rich areas in any such gene, and change the sequence to remove certain sequences, one of skill in the art would not immediately envision on what is otherwise any possible nucleic acid gene sequence as broadly claimed.” (Office Action, p.13). The Examiner cites the Grec et al. reference and indicates “that the structure of nucleic acid sequences, i.e. any gene for instance, is empirically determined and the structural elements of a gene in one species will have different regulatory sequences and different structural elements.” (Office Action, p.13). Applicants disagree.

The present invention is based on the finding that “in the presence of GT-rich base sequence, addition of poly (A) is determined in plants, subsequently mRNA is split at the position after 10-30 bp from the poly (A) signal, for example AATAAA like base sequence, then poly (A) is added by an action of poly (A) polymerase” (see page 8, lines 11-15 of the present application). Since the transcription of an mRNA from a heterologous nucleic acid and the addition of poly (A) proceed with RNA polymerase and other enzymes of the plant involved in transcription and poly (A) addition, the transcription and addition of poly (A) proceed independently from what is encoded in the heterologous nucleic acid. The present invention is therefore applicable to any heterologous nucleic acid irrespective of what is encoded in the nucleic acid.

Further, the instant specification clearly and explicitly teaches that the modification of a polyadenylation signal sequence and a GT rich sequence in the FRE1 gene does not interfere with expression of FRE1 in tobacco (see Example 9 entitled “Confirmation of Ferric-chelate Reductase”). Accordingly, the requirements for enablement are met in this case.

Nature of the Invention

According to the MPEP at 2164. 05(a), “whether the specification would have been enabling as of the filing date involves consideration of the nature of the invention, the state of the prior art, and the level of skill in the art. The initial inquiry is into the

nature of the invention, i.e., the subject matter to which the claimed invention pertains. The nature of the invention becomes the backdrop to determine the state of the art and the level of skill possessed by one skilled in the art.”

As to the nature of the invention, the Examiner does not comment on the nature of the invention. Applicants argue that given the disclosure and working examples, the nature of the invention is enabled as claimed.

Taken together, the teachings of the specification and knowledge of one of skill in the art enables one of skill in the art to practice the full scope of the claimed invention without having to resort to undue experimentation.

Applicants accordingly request that the rejection be reconsidered and withdrawn.

Written Description

The Examiner has rejected claims 1 - 16 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. The Examiner argues that “the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.” (Office Action, p.15). Applicants respectfully traverse the rejection.

The claims have been amended as set forth above.

The Examiner admits that “the specification as filed describes making modifications of the yeast FRE1, specifically making instant SEQ ID NO: 1, for use in plants. The specification describes transgenic tobacco plants expressing modified yeast FRE1...(that) exhibited functional enzymatic activity” and points out Figure 1 – 18 and Examples 1 – 9. (Office Action, p.16). The Examiner argues that “transgenic plants expressing any other modified gene sequences obtained from a different species are not described.” (Office Action, p.16). The Examiner argues further that “(t)he specification does not have adequate written description for genus of nucleic acid sequences comprising a coding sequence which has been modified to encode a functionally unaltered protein.” (Office Action, p.18).

The claims have been amended to recite specific polyadenylation signal sequences. Amended claim 1 recites "wherein the polyadenylation signal sequence is selected from the group consisting of ATTTA, NATAAA, ANTAAA, AANAAA, AATNAA, AATANA and AATAAN of which N is A, G, C or T." The claims have also been amended to recite "the GT rich sequence is 8 or more consecutive G and/or T nucleotides." The specification clearly describes factors that are required in a genus of nucleic acid sequences comprising a coding sequence which has been modified to encode a functionally unaltered protein, for example at paragraph [0134]:

it is necessary to design the sequence consisting of continued base sequence of 8 bases or more without containing sequence consisting of only G or T, and to design the sequence without containing not only a sequence of AATAAA but also a sequence, in which any one of bases thereof is replaced by another base.

Further, the instant claims require that the modification(s) of these sequences do not alter the amino acid sequence of the protein encoded by the heterologous nucleic acid. For Example, ATTTA could be modified to ATCTA or other sequences provided that the modification does not alter the amino acid sequence of the protein encoded by the heterologous nucleic acid. In view of the teachings of the specification and the vast amount of knowledge of codon degeneracy available to one of skill in the art, the claimed modified nucleic acid sequences could be constructed readily such that one of skill in the art would have recognized that applicant was in possession of the sequences as claimed.

Therefore, in view of the teachings of the instant specification, the claims clearly meet the written description requirement. Applicants respectfully request reconsideration and withdrawal of the rejection.

Rejection under 35 U.S.C. §102(b)

For the sake of brevity, these rejections are summarized below and addressed in combination.

Claims 1, 3-5, 7-8, 14, 15 and 16 are rejected under 35 U.S.C. §102(b) over Perlak et al. (PNAS, 88:3324-3328, 1991).

Claims 1, 5, 7-8, 13, 15 and 16 are rejected under 35 U.S.C. §102(b) over Nayak et al. (PNAS, 94:2111-2116, 1997).

Perlak

The Examiner states at page 22 of the Office Action that “Perlak et al. disclose a method of making a transgenic plant and seeds derived thereof comprising introducing and expressing a modified coding sequence cryIA(b) gene of *Bacillus thuringiensis* in transgenic tobacco and tomato plants. The transgenic plants exhibited improved insect resistance. The modification did not alter the amino acid sequence of the CryIA(b) protein. The modification of coding sequence for cryIA(b) comprised altering AATAAA and/or ATTTA sequences. Furthermore, the modification increased (increase is encompassed by difference) G and C content throughout the region of gene to be introduced, and modification was based on plant preferred codons without changing the amino acid sequence.”

Nayak

The Examiner states at page 23 of the Office Action that “Nayak et al. disclose a method of making a transgenic plant and seeds derived thereof comprising introducing and expressing a modified coding sequence cryIAC gene of *Bacillus thuringiensis* in transgenic rice (grass) plants. The transgenic plant exhibited improved insect resistance. The modification did not alter the amino acid sequence of the cryIAC protein. The modification of coding sequence for cryIAC comprised altering ATTTA sequences. Furthermore, the modification increased...G and C content throughout the region of gene to be introduced, and modification was based on plant preferred codons without changing the amino acid sequence.”

Applicants submit that for a determination of anticipation to be proper, the prior art reference must disclose each and every limitation of the claim. *Atlas Powder Company et al. v. IRECO, Incorporated et al.*, 190 F.3d 1342, 1347 (Fed. Cir. 1999).

The rejections are traversed. Neither of the cited documents teaches nor suggests the features of the present invention in any manner to sustain either one of the rejections.

Amended claim 1 requires “modifying...the GT rich sequence without altering the amino acid sequence of the protein encoded by the heterologous nucleic acid.”

Perlak et al. teach modifications of the coding sequence of insect control protein genes. Perlak does not teach or suggest “modifying the GT rich sequence” of the gene, as required by instant claim 1 and dependent claims thereof.

Figure 1 of Perlak et al. presents the DNA sequence of the WT and PM (partially modified) cryIA(b) genes wherein the differences between the genes are within the labeled boxed area (A-I). None of the modifications to the PM gene are modifications of a GT rich sequence, as required by instant claim 1.

Nayak et al. teach reconstruction of the cryIAc gene. Nayak et al. state on page 2112, right column, in the section entitled “Reconstruction of a Truncated cryIAc Gene” that “[t]he coding sequences of the cryIAc gene were reconstructed to remove potential RNA processing sequences and polyadenylation signals, and to optimize for more plant-preferred codon usage. Reconstruction was done essentially on the same line as that of Perlak et al”.

Nayak et al. do not teach or suggest “modifying the GT rich sequence” of the gene, as required by instant claim 1 and dependent claims thereof. Indeed, sequences of 8 or 9 consecutive G- or T- sequences remain in the reconstructed cryIAc nucleotide sequence shown in Fig. 3 of Nayak et al. (positions 529-537, positions 1759-1767).

In view of all of the above, Applicants respectfully request reconsideration and withdrawal of the rejections.

Rejection of Claim 9 under 35 U.S.C. §103(a)

Claim 9 is rejected under 35 U.S.C. §103(a) over Perlak et al. (PNAS, 88:3324-3328, 1991) in view of Kozak.

Perlak is discussed above in Applicants' response to the rejection under 35 U.S.C. §102(b).

Kozak

The Examiner states at pages 24 through 25 of the Office Action that "Kozak teach that Kozak sequence(s) increases the efficiency of binding of an eukaryotic mRNA to ribosome(s) and thus increasing the efficiency of translation initiation during protein synthesis...[i]t would have been obvious for one of...ordinary skill in the art at the time the claimed invention was made to modify Perlak et al. method for transforming a useful plant by adding a step of inserting Kozak sequence to the 5' end of translation initiation codon 'AUG' in bacterial cryIA(b) gene sequence."

The rejection is traversed. The cited documents, even in combination, fail to teach or suggest the features of the present invention in any manner sufficient to sustain the rejection.

Even if the references are combined, they do not provide the invention as claimed.

Applicants submit that even if the Perlak et al. reference is combined with the Kozak et al. reference, the combination of disclosures does not provide the invention recited in claim 9. That is, the recited combination lacks essential elements of the claimed invention.

As discussed above, the Perlak et al. reference does not teach or suggest "modifying the GT rich sequence" of a gene. Applicants submit that the Kozak et al. reference does not cure this deficiency. Kozak et al. presents an analysis of the role of flanking nucleotides in the recognition of the AUG initiator codon by eukaryotic ribosomes (see Abstract).

It is well-known that to establish a *prima facie* case of obviousness, three basic criteria must be met: (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there must be a reasonable expectation of success; and (3) the prior art reference(s) must teach or

suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). See MPEP § 2143.

There is no suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the cited references to make the claimed invention, nor is there a reasonable expectation of success. Accordingly, reconsideration and withdrawal of the rejection are requested.

In view of the above amendments and remarks, Applicants believe the pending application is in condition for immediate allowance.

FEE AUTHORIZATION

While no fees are believed to be due, the Commissioner is authorized to charge any fees associated with this submission to our Deposit Account, No. 04-1105, Reference 55022DIV(71526). Any overpayment should be credited to said Deposit Account.

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Respectfully submitted,

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